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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,596	02/11/2000	Mu-en Lee	05433-042001	6895

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Ingrid A Beattie PH.D JD
Fish & Richardson PC
225 Franklin St
Boston, MA 02110-2804

EXAMINER	
SCHMIDT, MARY M	
ART UNIT	PAPER NUMBER
1635	12

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,596	LEE ET AL.	
	Examiner	Art Unit	
	Mary Schmidt	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-23 is/are pending in the application.

4a) Of the above claim(s) 13-23 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election without traverse of claims 1-12 in Paper No. 11 is acknowledged.

2. Claims 13-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 11.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-12 are indefinite for failing to claim a final step which relates back to the preamble. For instance, the preamble of claim 1 introduces the limitation " a method of inhibiting formation of an atherosclerotic lesion" but does not recite a final method step after the open "comprising" language which teaches that the atherosclerotic lesion has been inhibited.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

> make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a methods of inhibiting formation of an atherosclerotic lesion in a mammal or inhibiting differentiation of a macrophage into a foam cell via administration to any species of mammal any compound which reduces expression of AFABP.

The claims broadly read on any sequence which could be considered an AFABP, from any mammalian organism, and any compound which could be considered an inhibitor of AFABP. The claims thus read on a broad scope of potential therapeutic agents which are not adequately described by way of structure in the specification or the art. The dependent claims further specify wherein the compound inhibits transcription of AFABP, bind to a cis-acting regulatory sequence of the AFABP, inhibit expression of the AFABP in macrophages but not in adipocytes or vice versa, wherein said inhibitor is an antisense nucleic acid, wherein said antisense nucleic acid molecule comprises at least 10 nucleotides the sequence of which is complementary to an mRNA encoding an AFABP polypeptide, wherein said antisense nucleic acid is a DNA operatively linked to a macrophage-specific promoter, wherein transcription of said DNA yields nucleic acid product which is complementary to an mRNA encoding an AFABP polypeptide.

Both the specification and the art teach a correlation between AFABP reduced expression and a reduction in atherosclerosis. The specification as filed specifically teaches knock-out mice which do not express the AFABP gene. However, neither the specification nor the art teach design of inhibitors specific for AFABP.

Applicant would not have been in possession of the claimed specific inhibitors of AFABP at the time the invention was made. Specifically, there is a high level of unpredictability in the art for design of inhibitors to a known target gene or protein. Factors such as specificity to the target molecule, accessibility of the target molecule in the whole organism, structure of the inhibitor, formulation of the inhibitor for use in whole organism, stability (lack of degradation) in the whole organism, etc. are significant design factors which are not taught in either the specification or the art for design of inhibitors such as those broadly claimed in the instant claims. The claims are also drawn to design of antisense to AFABP, but the claims broadly read on any possible AFABP from any organism, the sequences of which are not disclosed. To make an antisense to a known target gene, one skilled in the art must first know the sequence of the target gene. Secondly, one skilled in the art must know the accessible regions of the gene to which design of an antisense is possible (ie. there is no steric hindrance, for instance, inherent in the target region of the gene). Furthermore, for *in vivo*, whole organism use of antisense, there is a high level of unpredictability due to factors such as degradation and non-specific binding (see the arguments below under the 35 U.S.C. 112, first paragraph, enablement rejection). Since the specification discloses only a knock-out of the AFABP gene in mice, and there is no teaching in either the specification nor the

art for design of any inhibitor having a correlated function for use in any whole organism, Applicant would not have been in possession of the claimed inhibitors for use in the instantly claimed methods.

7. Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

See the brief description of the claimed invention above. The specification as filed teaches in Example 1 a knock-out of the AFABP in mice and the correlation between AFABP expression and atherosclerosis. However, as argued above in the 35 U.S.C. 112, first paragraph, written description, rejection, there is a high level of unpredictability in the art for design of inhibitors to a known target.

For example, in the case of design of antisense to a known target gene, there is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge

of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (in vivo) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro*, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

Similarly, it would be unpredictable in the art to design small molecule or protein inhibitors to AFABP for the therapeutic uses claimed since neither the art nor the specification

disclose methods of design of such inhibitors. Specifically, the same issues regarding delivery of small molecules or proteins to the whole organism exist as argued above for antisense molecules. Furthermore it would have required one of ordinary skill in the art "trial and error" experimentation to design a small molecule or protein inhibitor to AFABP since the designed inhibitor would necessarily be able to bind the AFABP in such a way as to result in its inhibition. Factors such as the degree with which such as inhibitor would inhibit the AFABP as well as the amount of total inhibition in the whole organism are factors which are not taught in the specification or the art.

One of skill in the art would not accept on its face the successful delivery of any claimed inhibitory molecule to AFABP *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of the claimed inhibitory molecules in whole organisms. Specifically the specification does not teach (1) stability of the inhibitors *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra*. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Katrina Turner*, whose telephone number is (703) 305-3413.

ANDREW WANG
PRIMARY EXAMINER

M. M. Schmidt
November 7, 2001